Oral Fluoroquinolones and the Risk of Retinal Detachment

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Context Fluoroquinolones are commonly prescribed classes of antibiotics. Despite numerous case reports of ocular toxicity, a pharmacoepidemiological study of their ocular safety, particularly retinal detachment, has not been performed.

Objective To examine the association between use of oral fluoroquinolones and the risk of developing a retinal detachment.

Design, Setting, and Patients Nested case-control study of a cohort of patients in British Columbia, Canada, who had visited an ophthalmologist between January 2000 and December 2007. Retinal detachment cases were defined as a procedure code for retinal repair surgery within 14 days of a physician service code. Ten controls were selected for each case using risk-set sampling, matching on age and the month and year of cohort entry.

Main Outcome Measure The association between retinal detachment and current, recent, or past use of an oral fluoroquinolone.

Results From a cohort of 989 591 patients, 4384 cases of retinal detachment and 43 840 controls were identified. Current use of fluoroquinolones was associated with a higher risk of developing a retinal detachment (3.3% of cases vs 0.6% of controls; adjusted rate ratio [ARR], 4.50 [95% CI, 3.56-5.70]). Neither recent use (0.3% of cases vs 0.2% of controls; ARR, 0.92 [95% CI, 0.45-1.87]) nor past use (6.6% of cases vs 6.1% of controls; ARR, 1.03 [95% CI, 0.89-1.19]) was associated with a retinal detachment. The absolute increase in the risk of a retinal detachment was 4 per 10 000 person-years (number needed to harm = 2500 computed for any use of fluoroquinolones). There was no evidence of an association between development of a retinal detachment and β-lactam antibiotics (ARR, 0.74 [95% CI, 0.35-1.57]) or short-acting β-agonists (ARR, 0.95 [95% CI, 0.68-1.33]).

Conclusion Patients taking oral fluoroquinolones were at a higher risk of developing a retinal detachment compared with nonusers, although the absolute risk for this condition was small.

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FLUOROQUINOLONES ARE ONE OF the most commonly prescribed classes of antibiotics. Their broad-spectrum antibacterial coverage and high-tissue distribution provide potency for a wide variety of community-acquired infections. Although fluoroquinolones are generally well tolerated, they have been associated with a wide array of adverse events such as dysglycemia,[1] cardiac arrhythmia,[2] and neuropsychiatric events.[3] Fluoroquinolones also have been linked to several forms of ocular toxicity such as corneal perforations,[4] optic neuropathy,[5] and retinal hemorrhages.[6] In 2011, the label for gemifloxacin was updated to include hemorrhage,[6] which includes retinal hemorrhage that was reported during postmarketing surveillance. A class-wide warning for fluoroquinolones also has been issued for tendon rupture,[7] which raises concerns for the effect of these drugs on connective tissue in the eye. Animal studies also provide evidence for retinal degeneration with use of fluoroquinolones.[8]

In the literature, there have been 3 reported cases of macular detachment with flumequine[9] and 1 reported case of retinal detachment[10] with ciprofloxacin. The putative mechanism behind a possible fluoroquinolone-induced retinal detachment may be through the destructive effect of the drugs on collagen and connective tissue.[11] Collagen fibers play a pivotal role in the structure and integrity of the vitreous body.[12] Thus, breakdown of collagen, possibly secondary to fluoroquinolone therapy, may promote the development of posterior vitreous detachment, leading to an increased risk of retinal detachment.

Retinal detachment is a serious medical emergency that may lead to irreversible vision loss. Up to 40% of those who experience this event may experience significant loss of visual acuity despite surgical intervention.[13] Given that oral fluoroquinolones are one of the

See also Patient Page.

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most prescribed classes of antibiotics, it is important that their full risk and safety profile be known. We conducted a pharmacoepidemiological nested case-control study to examine the association between oral fluoroquinolone use and the risk of retinal detachment.

METHODS

Data Sources

All residents of the province of British Columbia receive universal health coverage from the province's ministry of health. Data are captured by the British Columbia Linked Health Database, which contains linkable data files on patient demographics, hospital admissions[14] and discharges (including all hospital procedures), physician visits[15] (including all in-office procedures), and a comprehensive prescription drug database (PharmaNet).[16] PharmaNet captures information on all prescription drugs dispensed in the province and includes drug strength, quantity, and number of days of supply.

Quality checks on the data have been shown to be accurate with minimal misclassification of drug exposure.[17] The data are linkable through a unique identifier. The British Columbia Linked Health Database is one of the largest longitudinal databases with health care data on approximately 4.5 million residents. Because all Canadian residents are eligible for universal health care coverage, provincial databases provide a good representation of the Canadian population and have been used in numerous pharmacoepidemiological studies.[18,19]

Description of Cohort

The nested case-control cohort was comprised of all patients who had visited an ophthalmologist in the province of British Columbia between January 2000 and December 2007. Patients entered the cohort on the day of the first ophthalmologic visit and were followed up to diagnosis of retinal detachment, termination of health coverage, death, or termination of the study period, whichever came first.

Definition of Cases and Controls

Cases were identified as those with the first physician service code for retinal detachment after entry to the cohort. Incident cases were defined as those who had received an *International Classification of Diseases, Ninth Revision (ICD-9)* code 361 for retinal detachment, in addition to having received a procedure specific for retinal detachment such as surgery consisting of a scleral buckle, a vitrectomy, or a pneumatic retinopexy (British Columbia procedure codes 2194, 2199, 22196, respectively) within 14 days of the physician service code. The date of the service code was deemed the index date.

We made certain that no previous physician service claim (*ICD-9* 361.XX) or procedures for retinal detachment had been recorded from cohort entry to the index date (including *ICD-9* 361.06 and 361.07, which represent a prior retinal detachment). A diagnosis of endophthalmitis may increase the risk of retinal detachment. Although oral fluoroquinolone therapy is not common or the first-line treatment for this condition, we excluded patients who had received a physician service claim for endophthalmitis or those who had received a procedure code related to endophthalmitis, including an intravitreal antibiotic injection (British Columbia procedure code 2090) or a vitreous biopsy (British Columbia procedure code 2092).

Controls were selected using density-based sampling, an approach that allows for the close approximation of the odds ratio to the rate ratio.[20] For each case, we created a pool of potential eligible controls with no previous physician service claim or procedure code for retinal detachment who were followed up as long as the case (cohort entry to index date). From these eligible controls, 10 were selected at random and matched to a case by age (±1 year) and the month and year of cohort entry. Both cases and controls had to have had 1 year of prescription drug data that would allow us to assess prescription drug use.

Exposure Assessment

The main exposure of interest was use of oral fluoroquinolones. We identified all oral fluoroquinolones dispensed in the year prior to the index date including ciprofloxacin, gatifloxacin, grepafloxacin, levofloxacin, moxifloxacin, norfloxacin, ofloxacin, and trovafloxacin. Ophthalmic fluoroquinolones were excluded in both cases and controls because these drugs are used to treat a variety of ocular infections, which in turn may increase the risk of retinal detachments. This approach prevents against reverse causality bias. Furthermore, fluoroquinolone exposure was required to occur after a patient entered the nested cohort to ensure the drug exposure occurred after the initial ophthalmologic visit.

Retinal detachment was hypothesized to have an acute onset, and we categorized fluoroquinolone use based on the timing of the prescription termination date (date of dispensation plus number of days of supply) and the retinal detachment index date. Fluoroquinolone exposure was classified as current use, recent use, past use, and any use, which was a combination of all 3 exposure classifications.[21] Current users were defined as those with a prescription termination date overlapping with the index date. A recent user was defined as patient with a prescription termination date of 1 to 7 days prior to the index date, and a past user was defined as a patient with a prescription termination date of 8 to 365 days before the index date.

Physician billing codes were used as a proxy measure to examine the indication for fluoroquinolone use among patients who experienced a retinal detachment. We identified the first prescription dispensed for a fluoroquinolone prior to the index date. We specifically searched for the following therapeutic indications 14 days prior to the dispensation of the first fluoroquinolone prescription: respiratory tract infections, genitourinary tract infections, gastrointestinal tract infections, skin infections, and joint or bone in-

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Table 1. Characteristics of the Cases and Controls

	Cases (n = 4384)	Controls (n = 43 840)
Age at index date, mean (SD), y	61.1 (16.6)	61.1 (16.6)
Male sex, No. (%)	2551 (58.2)	1907 (43.5)
Follow-up duration, median (IQR), y	1.7 (0.3-3.1)	1.7 (0.3-3.1)
Comorbidities, No. (%)		
Cataract surgery	2025 (46.2)	14 862 (33.9)
Myopia[a]	162 (3.7)	1359 (3.1)
Diabetes[b]	675 (15.4)	5743 (13.1)
During year prior to index date, median (IQR), No.		
Prescriptions	11.0 (3.4-15.2)	10.0 (2.3-13.1)
Ophthalmologic visits	3.0 (1.4-4.4)	1.3 (0-11)

Abbreviation: IQR, interquartile range.
[a] Defined as a physician visit for myopia 1 year prior to the index date.
[b] Defined as the use of at least 1 medication for the treatment of diabetes 1 year prior to the index date.

Table 2. Cases of Retinal Detachment Stratified by the Type of Fluoroquinolone

Type of Fluoroquinolone	No. (%) of Cases (n = 445)
Ciprofloxacin	368 (82.7)
Levofloxacin	32 (7.2)
Norfloxacin	22 (4.9)
Moxifloxacin	18 (4.0)
Gatifloxacin	5 (1.1)

fections. Patients without a billing code for 1 of these 4 conditions were classified as having an indication of other. If more than 1 code was present during the 14-day period, the code appearing closest to the dispensation date was used.

As a quality measure, we tested the risk of retinal detachment in our study population with 2 distinct classes of medications that have not been associated with retinal detachment. First, we examined the association between retinal detachments and oral β-lactam antibiotics (all oral penicillins and cephalosporins), which is a different class of antibiotics that has not been shown to increase the risk of retinal detachments. Second, we examined the risk of retinal detachment with short-acting β-agonists, which is an unrelated class of drugs to fluoroquinolones that have limited systemic absorption.

Statistical Analysis

We examined study demographics for both cases and controls using descriptive statistics. Rate ratios (RRs) were computed to compare the incidence rate for retinal detachment for current fluoroquinolone users with nonusers. A conditional logistic regression model was constructed to adjust for covariates. In the model, we adjusted for sex, previous history of cataract surgery (as a measure for diagnosis of cataracts), myopia (defined as ≥1 physician service claim for myopia in the year prior to the index date), diabetes (use of ≥1 medication for the treatment of diabetes in the year prior to the index date), and the number of visits to an ophthalmologist 1 year prior to the index date. We also adjusted for the number of prescription drugs used in the year prior to the index date, which was intended as an overall measure of comorbidity.[22] To test the robustness of our results, we performed a sensitivity analysis[23] in which we examined the effect of an unmeasured confounder on the magnitude and direction of the RR. We computed a number needed to harm (absolute risk increase × 100) in which the absolute risk increase equaled the estimated incidence in the users (RR × incidence among nonusers) minus the incidence among nonusers.

Ethics approval was obtained from the behavioral ethics board of the University of British Columbia. All analyses were performed using SAS version 9.2 (SAS Institute Inc) using 2-sided tests of significance at the *P* value level of less than .05.

RESULTS

The cohort was composed of 989 591 patients. Within this cohort, 4384 cases of retinal detachment and 43 840 corresponding controls were identified. Cases were more likely to be male and were more likely to have myopia, diabetes, or have received cataract surgery (TABLE 1). As expected, 57% received a surgical procedure for a retinal detachment on the day of the diagnosis. Ciprofloxacin contributed to the most cases of retinal detachments followed by levofloxacin and norfloxacin (TABLE 2). Among the cases, respiratory tract infections and genitourinary tract infections were the most common indications for fluoroquinolone use in our study population (TABLE 3). Among current users, 8% had an indication that could not be determined using administrative data.

Current use of fluoroquinolones was associated with a significantly higher risk of developing a retinal detachment (adjusted RR [ARR], 4.50 [95% CI, 3.56-5.70]; TABLE 4). For current users, the mean (SD) number of days from the first fluoroquinolone prescription to the first event of a retinal detachment was 4.8 (4.8) days. No risk was observed among recent users (ARR, 0.92; 95% CI, 0.45-1.87) or past users (ARR, 1.03; 95% CI, 0.89-1.19). No risk was observed among current users of β-lactam antibiotics (ARR, 0.74; 95% CI, 0.35-1.57) or short-acting β-agonists (ARR, 0.95; 95% CI, 0.68-1.33). The absolute increase in the risk of a retinal detachment was 4 per 10 000 person-years (number needed to harm = 2500 computed for any use of fluoroquinolones).

Given the size of the demonstrated association, a group of residual confounders would need a cumulative association (odds ratio) with both the exposure and outcome on the magnitude of 10 to 15 to remove the significance of the effect found in the current study (eAppendix and eFigure at http://www.jama.com).

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COMMENT

This is the first study, to our knowledge, demonstrating that oral fluoroquinolones are associated with an increase in the risk of a retinal detachment. Current users of oral fluoroquinolones were nearly 5 times more likely to be diagnosed with retinal detachment than nonusers. As expected, no elevated risk for retinal detachment was found with users of β-lactam antibiotics or short-acting β-agonists compared with nonusers.

There have been 3 reported cases of macular detachment with flumequine, a first-generation fluoroquinolone not available in North America.[9] One report of retinal detachment secondary to ciprofloxacin has been reported to Health Canada.[10] It is possible that cases of retinal detachment with fluoroquinolones are underreported. Retinal detachment is a medical emergency mainly treated by an ophthalmologist with a subspecialty in retinal surgery.

The treatment objectives for this condition are prompt repair of the retina with the aim of preserving or restoring visual field and acuity. Because there are no previous studies associating oral fluoroquinolone use with retinal detachment, it is unlikely that treating retina surgeons suspected a possible link with oral fluoroquinolone use and retinal detachment, which may explain why more cases of retinal detachment secondary to fluoroquinolones have not been reported.

Our study has several strengths. We had a homogenous population of nearly 1 million patients who had visited an ophthalmologist, allowing for adequate power for this study. Retinal detachment is a sudden acute event that requires prompt surgical intervention. Access to specific procedure codes for retinal detachment in our data makes the possibility of misclassification for this condition unlikely.

Confounding by indication refers to a type of confounding that may arise in many pharmacoepidemiological studies of drug adverse events. This type of confounding refers to a situation in which physicians may be more likely to prescribe fluoroquinolones to patients at high risk for developing retinal detachment. However, this is unlikely in this study because the factors related to the prescribing of oral fluoroquinolones are not usually known to be associated with retinal detachment.[13] Other than endophthalmitis, cytomegalovirus retinitis is another type of ocular infection that may increase the risk of retinal detachments. Patients with AIDS who are more susceptible to this type of infection may receive oral fluoroquinolones for other AIDS-related infections. None of the patients in our study had a diagnosis of AIDS or cytomegalovirus retinitis.

The exact mechanism of retinal detachment with fluoroquinolones is unknown. The retina is a delicate structure within the eye attached to the cortical vitreous by a complex matrix of collagen fibers. Vitreous liquefaction, or syneresis, is a normal aging change of the vitreous that can result in retinal traction. Excessive traction can lead to retinal tears, which can lead to retinal detachment.[13] Conditions that

Table 3. Therapeutic Indications for Fluoroquinolone Use Among Patients With Retinal Detachment

	No. (%) of Patients With Retinal Detachment and Fluoroquinolone Use		
	Current (n = 145)	Recent (n = 12)	Past (n = 288)
Type of tract infection			
Respiratory	111 (77)	3 (25)	116 (40)
Genitourinary	13 (9)	3 (25)	77 (27)
Gastrointestinal	3 (2)	1 (8)	14 (5)
Skin infection	3 (2)	2 (17)	19 (7)
Joint or bone infection	3 (2)	1 (8)	18 (6)
Other[a]	12 (8)	2 (17)	44 (15)

[a] Indicates patients without physician billing codes for respiratory tract, genitourinary tract, gastrointestinal tract, skin, or joint or bone infection.

Table 4. Crude and Adjusted Rate Ratios for the Risk of Retinal Detachments With Oral Fluoroquinolones, β-Lactam Antibiotics, and Short-Acting β-Agonists

	No. (%)		Rate Ratio (95% CI)	
	Cases (n = 4384)	Controls (n = 43 840)	Crude	Adjusted[a]
No fluoroquinolone use[b]	3939 (89.8)	40 787 (93.0)	1 [Reference]	1 [Reference]
Fluoroquinolone use				
Any[c]	445 (10.2)	3053 (7.0)	1.55 (1.39-1.72)	1.39 (1.23-1.57)
Current[d]	145 (3.3)	275 (0.6)	5.55 (4.52-6.82)	4.50 (3.56-5.70)
Recent[e]	12 (0.3)	93 (0.2)	1.35 (0.74-2.47)	0.92 (0.45-1.87)
Past[f]	288 (6.6)	2685 (6.1)	1.13 (0.99-1.28)	1.03 (0.89-1.19)
β-Lactam antibiotic use				
Any	65 (1.5)	618 (1.4)	1.11 (0.99-1.24)	1.05 (0.93-1.18)
Current	9 (0.2)	106 (0.2)	0.85 (0.43-1.68)	0.74 (0.35-1.57)
Recent	0	16 (<0.1)	0	0
Past	56 (1.3)	496 (1.1)	1.13 (0.86-1.50)	1.03 (0.75-1.40)
Short-acting β-agonist use				
Any	160 (3.6)	1668 (3.8)	0.96 (0.81-1.13)	0.97 (0.81-1.16)
Current	44 (1.0)	440 (1.0)	1.00 (0.73-1.36)	0.95 (0.68-1.33)
Recent	7 (0.1)	73 (0.2)	0.96 (0.44-2.08)	0.94 (0.41-2.15)
Past	109 (2.5)	1155 (2.6)	0.94 (0.77-1.15)	0.98 (0.79-1.21)

[a] Adjusted for age, sex, cataracts, myopia, diabetes, number of prescriptions, and number of ophthalmologic visits.
[b] During the year prior to the index date.
[c] Use of 1 prescription at any time prior to the index date.
[d] A prescription termination date (date of dispensation plus the day supply) overlapping with the index date.
[e] A prescription termination date of 1 to 7 days before the index date.
[f] A prescription termination date of 8 to 365 days before the index date.

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interfere with connective tissue and collagen formation also increase vitreous liquefaction and have been shown to increase the risk of retinal detachment.[24]

Fluoroquinolones have been shown to interfere with collagen synthesis[25] and disrupt the extracellular matrix outside the retina, including the corneal matrix.[26] Oral fluoroquinolones have a relatively high bioavailability and a high volume of distribution. Only 2 doses of oral ciprofloxacin have been shown to provide adequate antibacterial concentration in the vitreous.[27] It is thus possible that damage from fluoroquinolones to collagen and connective tissue on the long bones may also translate to the same type of damage to other types of connective tissue including that of the vitreous and vitreous cortex.

The risk of retinal detachment from our study was only elevated among current users but not among recent or past users, indicating an acute adverse event. Given the limited number of animal studies or case reports specifically on fluoroquinolone-induced retinal detachment, it is difficult to infer the onset of fluoroquinolone-induced damage, which may lead to a retinal detachment. However, in one animal study, after 3 days of exposure to ciprofloxacin culture, collagen synthesis from tendon tissue was decreased by 48%.[28] The reported cases of tendon rupture with only 1 dose of a fluoroquinolone[11,29] further strengthen the hypothesis behind the acute toxicity of these drugs possibly to all types of connective tissue including ocular connective tissue.

Several large epidemiological studies have shown that oral fluoroquinolones are associated with an increase in the risk of Achilles tendon detachment.[21,30] Using a case-control study, van der Linden et al[30] have shown that current fluoroquinolone users were 7 times more likely to develop Achilles tendon rupture than nonusers (RR, 7.1; 95% CI, 1.7-29.1). The time to onset of tendon rupture has been reported to be between 2 and 31 days with a median time of 7 days.[11] This is in concordance with this study in which the time to onset of retinal detachment was 5 days with current users experiencing the highest risk of a retinal detachment. The incidence of a retinal detachment is estimated to be 12 per 100 000 patients annually in the United States.[13] Given an approximate exposure prevalence of 10%, and assuming a similar risk increase in the general population, the population attributable risk would be estimated to be approximately 4%. We estimate that 1440 cases of retinal detachment diagnosed annually in the United States may be attributed to oral fluoroquinolone use.

This study has several limitations. As with all pharmacoepidemiological studies using administrative data, the prescription drug history in our database only provide information on drug dispensing and not necessary drug intake. We did not have access to diagnostic information to verify the possible conditions for which fluoroquinolones may have been prescribed among the cases and could only rely on physician billing codes.

Ocular trauma is a leading cause of retinal detachment that we could not control for in this study. However, as demonstrated in the sensitivity analysis, a potential confounding effect of ocular trauma would have to be excessively large to change the results of this study. The nature of our data did not allow us to distinguish the type of retinal detachment based on procedure codes because the surgical procedure codes for all types of retinal detachment are the same. However, we suspect that the majority of retinal detachments in our data set are of the rhegmatogenous type, which are the most common type of retinal detachment requiring surgical intervention.[13] Moreover, because the study cohort was only composed of ophthalmologic patients, we could not assess the risk of retinal detachment secondary to fluoroquinolone use in the general population.

If this study population is enriched with persons at higher risk of retinal detachment, then it is possible that the absolute risk increase in the general population is lower than in this study, even if the relative risk estimate is generalizable to the general population. Finally, this study was designed to examine a class-effect association between fluoroquinolone use and retinal detachment, and it was not powered to examine this association among individual fluoroquinolones.

In summary, the results of this study are consistent with an association between fluoroquinolone use and the risk of retinal detachment. Future pharmacoepidemiological studies should be conducted to confirm or refute these findings.

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Study concept and design: Etminan, Forooghian, Brophy, Maberley.
Acquisition of data: Etminan, Maberley.
Analysis and interpretation of data: Etminan, Forooghian, Brophy, Bird, Maberley.
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Disclaimer: This study represents the opinions of the authors and not those of the US Food and Drug Administration.
Online-Only Material: The eAppendix and eFigure are available at http://www.jama.com.

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